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Enzyme replacement therapy with galsulfase for mucopolysaccharidosis type VI (Review)

Brunelli MJ, Atallah ÁN, da Silva EMK

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Enzyme replacement therapy with galsulfase for mucopolysaccharidosis type VI.
Cochrane Database of Systematic Reviews 2016, Issue 3. Art. No.: CD009806.
DOI: 10.1002/14651858.CD009806.pub2.

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[Intervention Review]

Enzyme replacement therapy with galsulfase for mucopolysaccharidosis type VI

Marcela Junqueira Brunelli[1], Álvaro N Atallah[2], Edina MK da Silva[3]

[1]Universidade Federal de São Paulo, São Paulo, Brazil. [2]Brazilian Cochrane Centre, Centro de Estudos de Saúde Baseada em Evidências e Avaliação Tecnológica em Saúde, São Paulo, Brazil. [3]Emergency Medicine and Evidence Based Medicine, Universidade Federal de São Paulo, São Paulo, Brazil

Contact address: Marcela Junqueira Brunelli, Universidade Federal de São Paulo, Dr Wladimir dos Santos Mello 122, São Paulo, São Paulo, 04112-030, Brazil. ma_junqueira@hotmail.com.

Editorial group: Cochrane Cystic Fibrosis and Genetic Disorders Group.
Publication status and date: New, published in Issue 3, 2016.
Review content assessed as up-to-date: 15 February 2016.

Citation: Brunelli MJ, Atallah ÁN, da Silva EMK. Enzyme replacement therapy with galsulfase for mucopolysaccharidosis type VI. *Cochrane Database of Systematic Reviews* 2016, Issue 3. Art. No.: CD009806. DOI: 10.1002/14651858.CD009806.pub2.

ABSTRACT

Background

Mucopolysaccharidosis type VI or Maroteaux-Lamy syndrome is a rare genetic disorder caused by the deficiency of arylsulphatase B. The resultant accumulation of dermatan sulphate causes lysosomal damage.

The clinical symptoms are related to skeletal dysplasia (i.e. short stature and degenerative joint disease). Other manifestations include cardiac disease, impaired pulmonary function, ophthalmological complications, hepatosplenomegaly, sinusitis, otitis, hearing loss and sleep apnea. Intellectual impairment is generally absent. Clinical manifestation is typically by two or three years of age; however, slowly progressive cases may not present until adulthood.

Enzyme replacement therapy with galsulfase is considered a new approach for treating mucopolysaccharidosis type VI.

Objectives

To evaluate the effectiveness and safety of treating mucopolysaccharidosis VI by enzyme replacement therapy with galsulfase compared to other interventions, placebo or no intervention.

Search methods

Eletronic searches were performed on the Cystic Fibrosis and Genetic Disorders Group's Inborn Errors of Metabolism Trials Register, in CENTRAL, MEDLINE, LILACS, the Journal of Inherited Metabolic Disease and ClinicalTrials.gov.

Date of the last search of the Cystic Fibrosis and Genetic Disorders Group's Inborn Errors of Metabolism Trials Register: 05 February 2016.

Selection criteria

Randomized and quasi-randomized controlled clinical studies of enzyme replacement therapy with galsulfase compared to other interventions or placebo.

Data collection and analysis

Two authors independently screened the studies, assessed the risk of bias and extracted data.

Main results

One study was included involving 39 participants who received either enzyme replacement therapy with galsulfase (recombinant human arylsulphatase B) or placebo. This small study was considered to be of overall unclear quality, since the authors did not report how both the allocation generation and concealment were performed.

The key finding at 24 weeks in the 12-minute walk test was a statistically significant mean difference of 92.00 meters between the two groups in favour of the galsulfase group (95% confidence interval 11.00 to 172.00). While week 24 results for the three-minute stair climb demonstrated some improvement in the treatment group as compared to the placebo group, this was not significant, mean difference 5.70 (95% confidence interval -0.10 to 11.50).

A significant decrease in the urinary glycosaminoglycan levels was observed in favour of the galsulfase group at 24 weeks, mean difference -227.00 (95% confidence interval -264.00 to -190.00).

In general, the dose of galsulfase was well tolerated and there were no significant differences in relation to adverse events. These events include drug-related adverse events, serious and severe adverse events, those during infusion, drug-related adverse events during infusion, and deaths. More infusion-related reactions were observed in the galsulfase group and were managed with interruption or slowing of infusion rate or administration of antihistamines or corticosteroids drugs. No deaths occurred during the study.

Authors' conclusions

The results of one small study (based on 24-week randomised phase of the study and prior to the open-label extension) demonstrated that galsulfase is more effective than placebo in people with MPS VI, with significant improvements in the 12-minute walk test and a reduction in urinary glycosaminoglycans.

There were no significant changes in cardiac or pulmonary functions, liver or spleen volume, overnight apnea-hypopnea, height and weight, quality of life and adverse effects.

Further studies are needed to obtain more information on the long-term effectiveness and safety of enzyme replacement therapy with galsulfase.

PLAIN LANGUAGE SUMMARY

Enzyme replacement therapy with galsulfase for mucopolysaccharidosis type VI

Review question

We reviewed the evidence about the effectiveness and safety of treating mucopolysaccharidosis type VI by enzyme replacement therapy with galsulfase (a manufactured version of the enzyme arylsulphatase B) compared to other interventions, no intervention or placebo.

Background

Mucopolysaccharidosis type VI is a rare genetic disorder where there is a lack of the enzyme arylsulphatase B. It is a progressive and life-limiting condition with a range of symptoms, which may include coarse facial features, reduced joint mobility, short stature and problems with the eyes, lungs and heart.

Prior to enzyme replacement therapy, only symptoms could be treated and not the underlying condition. Treatment with enzyme replacement therapy has allowed the missing enzyme to be replaced with the aim to reduce the effects of the disease and prevent it progressing.

Search date

The evidence is current to: 05 February 2016.

Study characteristics

The review includes one study with 39 people with mucopolysaccharidosis type VI aged between five and 20 years old. The study compared galsulfase to placebo (a substance which contains no medication) and people were selected for one treatment or the other randomly. The study lasted for 24 weeks (with an open-label extension period of an additional 24 weeks).

Key results

Given that there is only one small study included, the evidence for this treatment is limited. The included study showed that motor function improved in people who had received galsulfase, especially in their ability to walk. There was also an improvement in the results of urine tests, which showed lower levels of the chemicals associated with MPS VI (glycosaminoglycan levels). These results were seen in a short study and may reflect only short-term effects. There were no significant differences between treatment with galsulfase and placebo in relation to adverse effects.

More research is required to study the long-term effects on heart and lung function, quality of life and survival.

Quality of the evidence

The methods of the study design were not clearly described and the impact of this on possible bias is unclear.

BACKGROUND

A glossary of terms is available (Appendix 1).

Description of the condition

Mucopolysaccharidosis type VI (MPS VI), also known as Maroteaux-Lamy syndrome, is an autosomal recessive disease. It is caused by deficiency of N- acetylgalactosamine 4-sulphatase (arylsulphatase B). This results in a cascade of problems including lysosomal damage and accumulation of dermatan sulphate (Cardoso-Santos 2008; Maroteaux 1963). It has been estimated that approximately 1 in 340,000 births are affected with MPS VI (Lowry 1990; Meikle 1999; Nelson 1997; Pinto 2004).

The clinical presentation varies based on age of onset and rate of disease progression. The speed and intensity of damage caused by the disease varies between the slowly and rapidly progressing forms. Short stature and degenerative joint disease are consequences of the skeletal dysplasia. Other clinical manifestations include cardiac valve disease, reduction in pulmonary function, hepatosplenomegaly, sinusitis, otitis, hearing loss, sleep apnea, corneal clouding, inguinal or umbilical hernia and carpal tunnel disease. Intellectual impairment is generally absent (Giugliani 2007; Valayannopoulos 2010).

Clinical treatment of MPS VI has been based on improving some of the most dangerous and debilitating manifestations of the disease (i.e. continuous positive airway pressure (CPAP) for sleep apnea). Currently, palliative treatment still has a role, along with other treatment options, such as bone marrow or hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT) (Giugliani 2007; Neufeld 2001; Valayannopoulos 2010).

The main indication of HSCT is for people with cognitive impairment (i.e. severe form of MPS I) and has been recommended in rare cases of MPS VI. Despite of the improvements of leukocyte arylsulphatase B and urinary glycosaminoglycans levels, no impact in skeletal abnormalities were observed in the long-term follow-up case studies (Valayannopoulos 2010). In MPS VI it has been considered a secondary option since the risks of the procedure do not appear to exceed the benefits (Giugliani 2007).

Description of the intervention

Galsulfase is an enzyme manufactured by recombinant DNA technology that uses a mannose-6-phosphate receptor to bind to the cell surface, transporting the enzyme into the lysosomes, in order to supply arylsulphatase B (Valayannopoulos 2010).

Enzyme replacement therapy with galsulfase is currently recommended as weekly intravenous infusions, delivered over a period of four hours, at a recommended dose of 1 mg/kg body weight. Adverse reactions have been observed typically being anaphylactic. Reaction symptoms include dyspnea, rigours, nausea, chest pain, pyrexia, exanthem, urticaria, abdominal pain and swelling. Infusion-related reactions can be managed by the use of antihistamines or steroids (with or without antipyretics) prior to infusion (Giugliani 2007).

How the intervention might work

Galsulfase treatment aims to replace the deficient arylsulphatase B and thus limit, stop or reverse disease progression and improve symptoms related to endurance and pulmonary function (Decker 2010). Due to poor skeletal vascularisation and the presence of the blood-brain barrier it is less effective for treating skeletal and central nervous system features (Giugliani 2007).

Why it is important to do this review

Even though most experts recommend ERT as first-line treatment, most nations do not have an established public health policy that considers ERT for the management of MPS VI, especially due to the high costs of the treatment (Giugliani 2007). This review may be used to help decision- and policymakers.

OBJECTIVES

To evaluate the effectiveness and safety of treating MPS VI by ERT with galsulfase compared to other interventions, no intervention or placebo.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and quasi-randomized controlled clinical studies.

Types of participants

Individuals with MPS VI of any age and any degree of disease severity. Diagnosis should be established by enzyme assay in leukocytes, fibroblasts or plasma or genetic mutation results.

Types of interventions

Enzyme replacement therapy with galsulfase at any dose for a period of at least one month compared to other interventions, placebo, or no intervention.

Types of outcome measures

Primary outcomes

1. Functional test
   i) 12-minute walk test (12MWT)
   ii) 3-minute stair climb (3MSC)
   iii) other validated measures of functionality used by trial authors (i.e. 6-minute walk test (6MWT))

Secondary outcomes

1. Lung function
   i) forced expiratory volume at one second (FEV_1)
   ii) forced vital capacity (FVC)
   iii) total lung capacity (TLC)
2. Cardiac function (assessed by echocardiography)
3. Change in urinary excretion of glycosaminoglycans (GAGs)
4. Z scores for height and weight
5. Overnight apnea-hypopnea index (AHI)
6. Quality of life (using a validated scoring system, e.g. SF-36)
7. Joint mobility (using a validated scoring system, e.g. Joint Range of Motion (JROM), grip and pinch strength tests)
8. Liver and spleen volume (measured by ultrasound or computed tomography (CT) scan of the abdomen)
9. Audiology assessment (using a validated scoring system, e.g. Pure-Tone Testing, auditory brainstem response (ABR), otoacoustic emissions (OAEs))
10. Adverse effects and toxicity of treatment

Search methods for identification of studies

Electronic searches

Relevant trials were identified by searching the Cochrane Cystic Fibrosis and Genetic Disorders Group's Inborn Errors of Metabolism Trials Register using the term: mucopolysaccharidosis.

The Cochrane Cystic Fibrosis and Genetic Disorders Group's Inborn Errors of Metabolism Trials Register was compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated with each new issue of *The Cochrane Library*), weekly searches of MEDLINE, LILACS database and the prospective handsearching of one journal - *Journal of Inherited Metabolic Disease*. Unpublished work were identified by searching through the abstract books of the Society for the Study of Inborn Errors of Metabolism conference and the SHS Inborn Error Review Series. For full details of all searching activities for the register, please see the relevant section of the Cystic Fibrosis and Genetic Disorders Group Module.

Date of last search: 05 February 2016.

We also undertook additional searches of the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, LILACS (http://lilacs.bvsalud.org/) (Appendix 2; Appendix 3; Appendix 4) and ClinicalTrials.gov (http://www.clinicaltrials.gov).

Searching other resources

We scrutinized the reference lists of any identified relevant studies for additional citations and contacted specialists in the field, first authors of the included study and pharmaceutical manufacturers for any relevant unpublished data.

Data collection and analysis

Selection of studies

One author verified all identified reports and extracted the relevant information and data. To ensure reliability of the selection of studies, one of the remaining authors independently re-verified these reports. If any disagreement or doubts occurred, we discussed this until consensus was reached.

Data extraction and management

Two authors independently extracted all data. We resolved differences by discussion and if necessary, we contacted the study authors to resolve any outstanding issues. We identified exclusions and dropouts. If any relevant information or data were not available (even with the study authors' feedback), we identified these as missing data. We entered the data into the Review Manager software (RevMan 2014).

Assessment of risk of bias in included studies

Two authors independently evaluated the selected studies using the recommendations as described in the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We expressed the domains below simply as having either a low, high or unclear risk of bias:

1. random sequence generation;
2. concealment of allocation;
3. blinding of: participants, personnel, outcome assessment;
4. incomplete outcome data;
5. selective reporting;
6. other potential sources of bias.

Measures of treatment effect

We calculated treatment effects using the risk ratio (RR) with 95% confidence intervals (CIs) for dichotomous data.
For continuous outcomes, we estimated the mean difference (MD) and 95% CIs. We used the generic inverse variance method (GIVM) for this type of outcome in the studies that only reported odds ratios or relative risks and standard errors (SEs).

Unit of analysis issues

We did not identify studies with a cross-over design. In future updates, we intend to follow the recommendations of Elbourne, undertaking a paired analysis, using a t-test in data obtained by each participant and comparing the treatment interventions (Elbourne 2002). For cluster-randomised studies, in the analyses, if possible, we will attempt to account for any unit of analysis error, considering the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) by using an estimate of the intra-cluster correlation co-efficient (ICC) derived from the study (if possible), from a similar study or from a study of a similar population.

Dealing with missing data

In the case of absent data or queries about missing data, the first author (MJB) contacted the study authors.

Assessment of heterogeneity

We did not evaluate the heterogeneity, because we identified only one study. In future updates, the clinical heterogeneity of the studies will be quantified using the Chi^2 test and the I^2 statistic to illustrate the percentage of the variability in effect estimates resulting from heterogeneity rather than sampling error (Higgins 2003), where I^2 values may indicate, as follows:
0% to 40%: might not be important;
30% to 60%: may represent moderate heterogeneity;
50% to 90%: may represent substantial heterogeneity;
75% to 100%: considerable heterogeneity.

Assessment of reporting biases

In future updates, we intend to build a funnel plot if there are a sufficient number of studies (i.e. 10). If the funnel plot is asymmetrical, this may indicate publication bias. However, there are other reasons for asymmetry including heterogeneity, outcome reporting bias and small study effects.

Data synthesis

We used the fixed-effect model for meta-analysis of data. For future updates, we will consider using a random-effects model should there be substantial heterogeneity between the studies.

Subgroup analysis and investigation of heterogeneity

In future updates, if further studies are added and we identify heterogeneity between them, we intend to undertake subgroup analyses according to:

1. disease progression (slowly and rapidly advancing forms) and;

2. enzyme dose.

Sensitivity analysis

Sensitivity analyses were not carried out as only a single study was identified. In future updates, if there are a sufficient number of eligible studies included (10 or more), we will undertake a sensitivity analysis to assess the robustness of the results. For this evaluation we considered the risk of bias for: allocation concealment; method of blinding; rates of withdrawal for each outcome; other study design (Deeks 2011). We aim to perform a sensitivity analysis by considering studies with a high risk of bias in these domains against those with a low or unclear risk of bias.

RESULTS

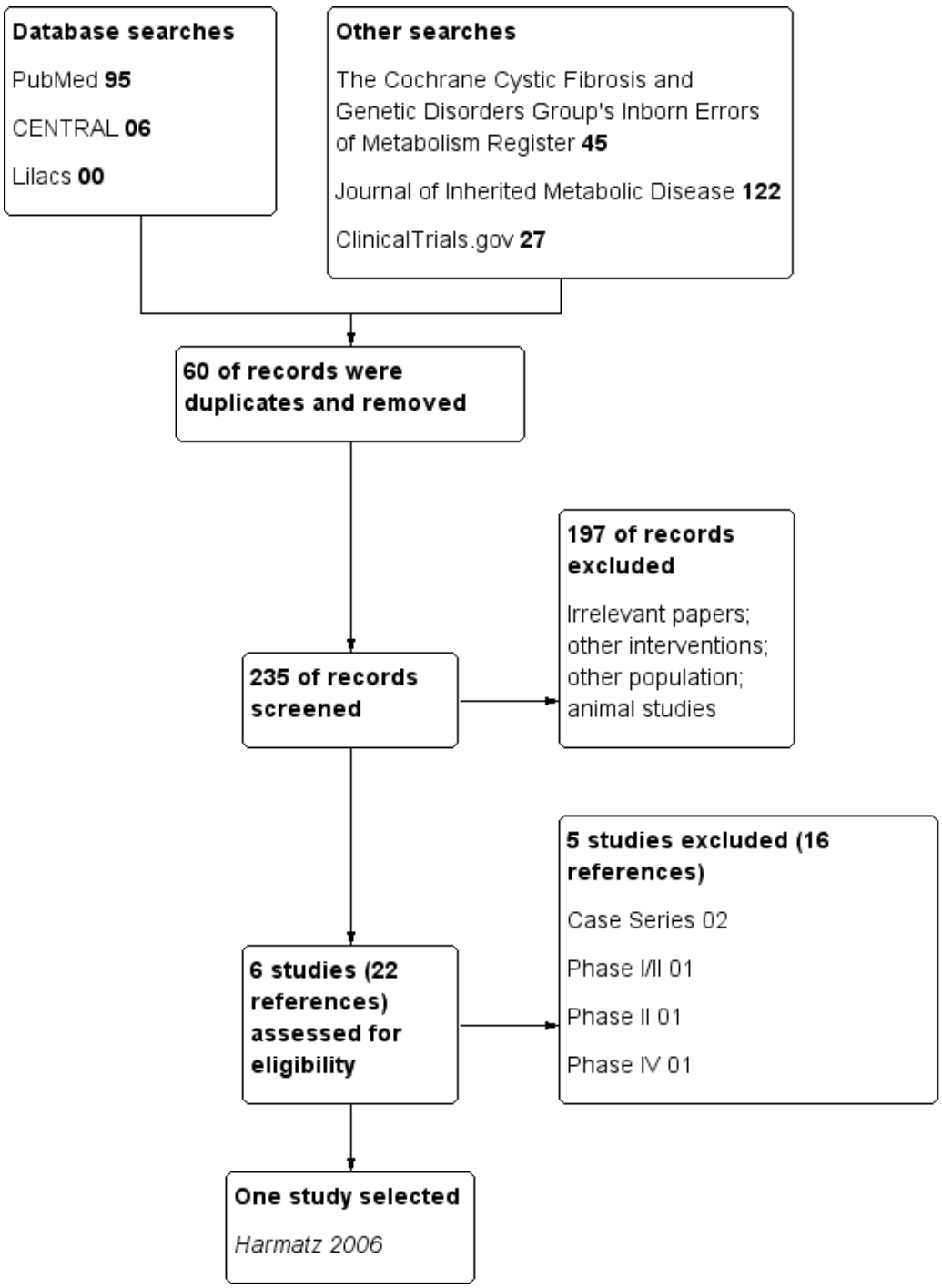
Description of studies

See: Characteristics of included studies ; Characteristics of excluded studies.

Results of the search

A total of 295 references were identified through the search strategies, of which 289 were excluded (i.e. did not the meet inclusion criteria or were duplicate references). Full texts of six studies were obtained for further assessment. After a detailed reading, five studies were excluded (*see* Characteristics of excluded studies) (Bagewadi 2008; Harmatz 2004; Harmatz 2005; Harmatz 2013; Pitz 2009). Only one study (six references) was included in this review. Refer to the flow diagram for the details of the search process (Figure 1).

Figure 1. Study flow diagram.



Included studies

One study met the inclusion criteria of this review (Harmatz 2006).

Design

The selected study was a phase III, randomized, multicenter, placebo-controlled, double-blind study and evaluated the efficacy and safety of galsulfase in people with MPS VI (Harmatz 2006). A 24-week open-label extension to the study was conducted and all participants receiving placebo solution in the first 24 weeks commenced treatment with recombinant human N-acetylgalactosamine 4-sulfatase (recombinant human arylsulphatase B) (rhASB) solution. As this phase was not re-randomised the results are not included in the review.

Sample sizes

A total of 39 participants were included (Harmatz 2006).

Setting

Participants were enrolled at six clinical sites, but no further details were provided (Harmatz 2006).

Participants

The 39 participants were over seven years of age with either biochemical or genetic proof of MPS VI, with the ability to walk without assistance at least five meters and no more than 270 meters in the first six minutes, or no more than 400 meters in a 12-minute walk test. Exclusion criteria were clinically significant spinal cord compression, a medical condition or other circumstance that could interfere with study compliance.

Participants were randomised into two groups: 19 in the rhASB group (7 males and 12 females, mean age 13.7 years); 20 in the placebo group (six males and 14 females, mean age 10.7 years).

Interventions

Participants were randomised to receive intravenous infusions of rhASB 1.0 mg/kg or a placebo solution over 24 weeks administered over four hours once weekly with 2.5% of the total dose infused during the first hour and the remainder over the next three hours (Harmatz 2006). A pre-medication with either diphenhydramine 0.5 mg/kg or promethazine 0.15 mg/kg was administrated to all participants.

Outcomes

The study considered the following outcomes:

1. 12MWT;
2. 3MSC,
3. Level of urinary GAG excretion;
4. Others outcomes analysed:

i) assessments of joint pain, joint stiffness, and physical energy level;

ii) assessment of joint ROM;

iii) assessment of hand dexterity as evidenced by the number of coins picked up in one minute;

iv) clinical parameters including pulmonary and cardiac, and ophthalmologic monitoring tests.

Safety was determined by considering adverse events, monitoring of changes in laboratory parameters (chemistry, hematology, urinalysis, thyroid function) and assessment of electrocardiography (Harmatz 2006).

Excluded studies

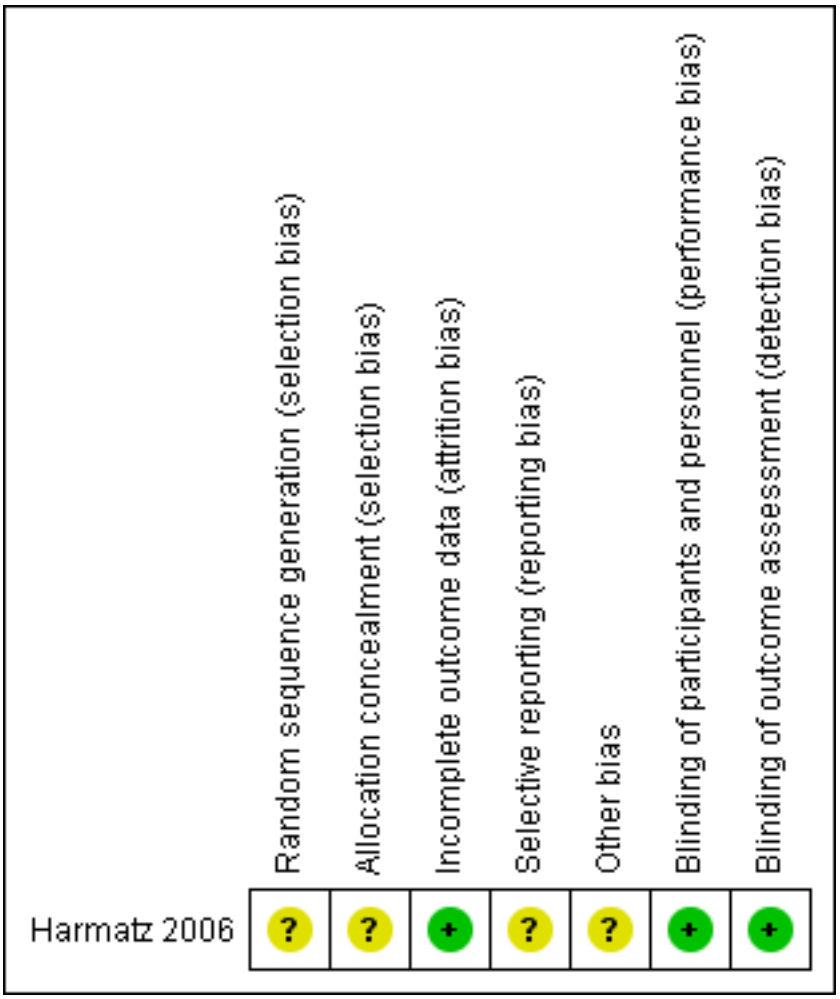
See Characteristics of excluded studies table.

We excluded five studies because they did not meet the inclusion criteria. The Harmatz 2004 and 2005 studies were phase I/II and phase II clinical studies, respectively (we did not consider studies that evaluated safety and dosing requirements) (Harmatz 2004; Harmatz 2005); two publications were case-series studies (Bagewadi 2008; Pitz 2009); and one was an evaluation of the efficacy and safety of two dosing regimens of the intervention without a control group (Harmatz 2013).

Risk of bias in included studies

See the 'Risk of bias' summary (Figure 2).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Genration of the randomisation sequence

The study was described as randomised, but the method of randomisation was not provided. We have classified this domain as having an unclear risk of bias.

Allocation concealment

No description of allocation concealment was reported, we have therefore classified this domain as having an unclear risk of bias.

Blinding

The study stated that investigators and staff were not informed of the original treatment assignments and did not participate in the efficacy assessments. We classified this domain as having a low risk of bias.

Incomplete outcome data

The study reported that safety analyses included all participants who received at least one dose of the intervention and the efficacy analyses included all randomised participants (intention-to-treat analysis). The trial author also declared that 11 individuals, who did not fulfil inclusion criteria (seven exceeded the walk distance eligibility entry criteria at screening, three were under seven years

of age, and one had experienced a failed bone marrow transplant 11 years earlier) were not excluded (did not interfere with study compliance) and were also randomised. Authors mentioned that one participant withdrew from the study after four infusions of placebo for reasons unrelated to treatment. We considered this domain as having a low risk of bias.

Selective reporting

The study only presented the results for the following outcomes: 12MWT; 3MSC; level of urinary GAG excretion; and pulmonary function. Results of others outcomes analysed (joint pain, hand dexterity and cardiac and ophthalmologic parameters) were not provided and authors only declared that rhASB had no effect in these endpoints. We considered this domain as having an unclear risk of bias.

Other potential sources of bias

Despite randomization, the characteristics of the study participants were not similar between the two groups (participants in the placebo group were, on average, younger, shorter, and weighed less than those in the rhASB group, the authors declared that none of these differences was statistically significant). No other potential sources of bias were detected. We considered this domain as having an unclear risk of bias.

Effects of interventions

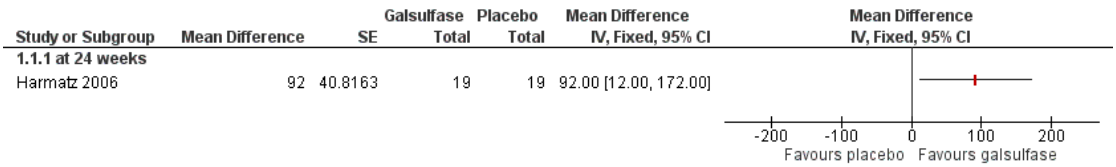
Primary outcomes

1. Functional test

a. 12-minute walk test (12MWT)

This was reported in the included study, where the intervention group had a substantial increase in walk distance during the first six weeks of treatment, with a sustained, stable improvement that remained the same between week 18 and week 24. At the end of the randomisation period (24 weeks), the intervention group demonstrated significant improvement, compared to placebo with a MD of 92.00 meters (95% CI 12.00 to 172.00) in the change from baseline; P = 0.03 (Analysis 1.1; Figure 3).

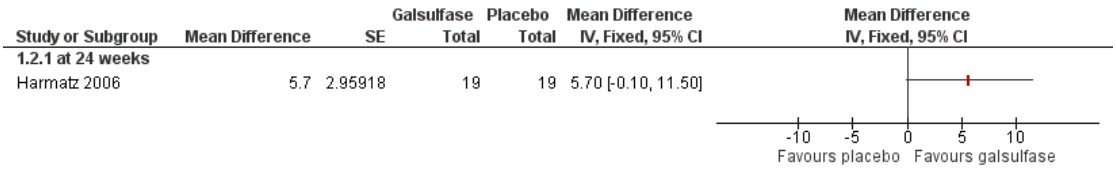
Figure 3. Forest plot of comparison: 1 Galsulfase verus placebo, outcome: 1.1 12MWT.



b. 3-minute stair climb (3MSC)

At week 24, the study authors reported a greater improvement in the treatment group than in placebo; however, when entered into our analysis, while the results in the rhASB group demonstrated some improvement compared to the placebo group in a longitudinal analysis, this was not significant, MD 5.70 (95% CI -0.10 to 11.50); P = 0.062. (Analysis 1.2; Figure 4).

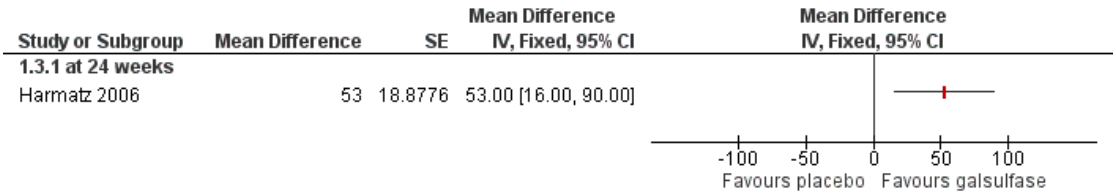
Figure 4. Forest plot of comparison: 1 Galsulfase verus placebo, outcome: 1.2 3MSC.



c. Other validated measures of functionality

The 6MWT was not considered as an endpoint of the included study (Harmatz 2006). However, the authors reported that the rhASB group was superior to the placebo group in distance walked at the 6-minute time point during the 12MWT test, with a MD of 53.00 meters at week 24 (95% CI 16.00 to 90.00), considering this as supportive of the primary endpoint; P = 0.007 (Analysis 1.3; Figure 5).

Figure 5. Forest plot of comparison: 1 Galsulfase verus placebo, outcome: 1.3 6MWT.



Secondary outcomes

1. Lung function

a. forced expiratory volume at one second (FEV_1)

It was reported in the primary paper that there was no difference in FEV_1 during the study, but no data or P values were reported (Harmatz 2006).

b. forced vital capacity (FVC)

No improvement of FVC was observed (Harmatz 2006). There was no significant difference in the absolute change in FVC at week 24 for the rhASB group, MD -0.01 (95% CI -0.08 to 0.06) (Analysis 1.4).

c. total lung capacity (TLC)

This outcome was not reported.

d. maximum voluntary ventilation (MVV)

This parameter was evaluated to determine any improvement in rib-cage excursion as a result of improved flexibility or increased strength (Harmatz 2006). The results were not statistically significant, MD 1.90 (95%CI -2.05 to 5.85) (Analysis 1.4).

2. Cardiac function

This outcome was not reported (Harmatz 2006).

3. Change in glycosaminoglycans (GAGs) urinary excretion

The results showed a significant difference in favour of the rhASB group at week 24, MD -227.00 (95% CI -264.00 to -190.00) (Harmatz 2006) (Analysis 1.5).

4. Z scores for height and weight

This outcome was not reported (Harmatz 2006).

5. Overnight apnea-hypopnea index (AHI)

This outcome was not reported (Harmatz 2006).

6. Quality of life

This outcome was not reported (Harmatz 2006).

7. Joint mobility

It was reported in the primary paper that there was no difference in joint mobility during the study, but no data or P values were reported (Harmatz 2006).

8. Liver and spleen volume

This outcome was not reported Harmatz 2006).

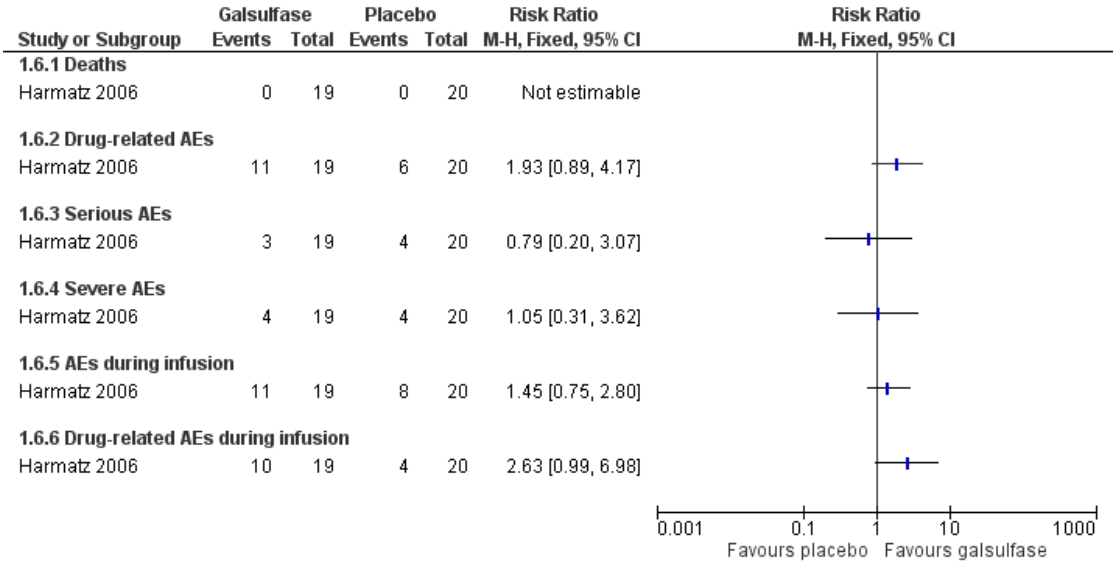
9. Audiology assessment

This outcome was not reported Harmatz 2006).

10. Adverse effects and toxicity of treatment:

At week 24 adverse events were divided into the following subcategories (Harmatz 2006) (Analysis 1.6; Figure 6). There were no significant differences observed for:

Figure 6. Forest plot of comparison: 1 Galsulfase verus placebo, outcome: 1.6 Adverse events.



- deaths: nil in either group;
- drug-related adverse events, RR 1.93 (95% CI 0.89 to 4.17);
- serious adverse events, RR 0.79 (95% CI 0.20 to 3.07);
- severe adverse events, RR 1.05 (95% CI 0.31 to 3.62);
- adverse events during infusion, RR 1.45 (95%CI 0.75 to 2.80);
- drug-related adverse events during infusion, RR 2.63 (95% CI 0.99 to 6.98).

More infusion-related reactions occurred in the rhASB group. These were easily managed with interruption or slowing of infusion rate or administration of an extra-dose of antihistamines or corticosteroids. Other adverse effects were similar in both

groups (i.e. rigours, pyrexia, chest pain, dyspnea, abdominal pain, headache) and were most likely related to the diphenhydramine premedication and the participant's poor respiratory status.

DISCUSSION

Summary of main results

The results of the Harmatz study showed some benefits in those treated with recombinant human arylsulphatase B (rhASB) (galsulfase) in comparison to those who received placebo (Harmatz 2006). It is important to realize that the characteristics of the study participants were not similar between the two groups (participants in the placebo group were, on average, younger, shorter, and weighed less than those in the rhASB group, the authors declared that none of these differences was statistically significant).

There was significant improvement in the 12-minute walk test (12MWT) in the rhASB group as compared to placebo based on the longitudinal analysis, mean difference (MD) 92.00 meters (95% confidence interval (CI) 12.00 to 172.00). Although the study has not considered the 6-minute walk test (6MWT) as an endpoint, an analysis at week 24 was described as supportive of the 12MWT results, showing significant differences in this time point (6 minutes) by 53 meters (95% CI 16.00 to 90.00).

While the 3-minute stair climb (3MSC) test did not show statistically significant improvement, the results were better in the rhASB group as compared to the placebo group, MD 5.70 (95% CI -0.10, 11.50).

Pulmonary function was evaluated in long-term enzyme replacement therapy (ERT) treatment with rhASB. Pulmonary tests, such as forced vital capacity (FVC), forced expiratory volume at one second (FEV_1) and in a subset of participants, maximum voluntary ventilation (MVV), were analysed. During the 24 weeks of the randomised period, FVC, FEV_1 and MVV showed no significant differences from baseline.

A reduction of 75% from baseline in glycosaminoglycans (GAG) levels were observed at week 24 in the rhASB group. This was maintained between week 25 and week 48 (in the open-label extension phase of the study), with all participants experiencing a similar decrease.

The Harmatz study reported no data for other tertiary endpoints (assessments of joint pain, joint stiffness, physical energy level and clinical parameters such as ophthalmologic monitoring tests). The authors stated there did not appear to be any difference of effect between groups, but did not publish the participants' results, indicating a potential 'reporting bias'.

In general, treatment with rhASB was well tolerated by participants during the 24 weeks of the randomised study. All but one of the participants in the study developed IgG antibody to rhASB after 24 weeks of drug infusion.

Overall completeness and applicability of evidence

The evidence for the efficacy of ERT with rhASB is limited given there is only one relevant study that provided data on the short-term efficacy and safety of this treatment. The study did, however, highlight significant improvements in the 12MWT (and the 6MWT as a supportive outcome) and urinary GAG levels (Harmatz 2006). Support for improvement in endurance was also seen with the results of the 3MSC, although these results were not clinically significant.

Quality of the evidence

The included study was considered to be of unclear quality, since the authors did not report how both the allocation generation and concealment were performed. Furthermore, the number of participants included was small and the follow-up time was short. Important outcomes were not determined, e.g. respiratory capacity and cardiac function, quality of life and mortality.

Potential biases in the review process

We followed the criteria listed within the 'Assessment of risk of bias' section to ensure the risk of bias was minimized during trial selection.

Agreements and disagreements with other studies or reviews

Other non-randomized studies evaluating the ERT with galsulfase are available. Due to the safety of the drug, Bagewadi suggested home ERT with galsulfase, although, a detailed management plan for potential anaphylaxis and infusion-associated reaction (IAR) has to be adopted (Bagewadi 2008). Close monitoring is required during infusions in those with a history of IAR, especially given most people with MPS VI have cardiac and respiratory system impairment. Dogan reported the first case of an individual with MPS VI who developed thrombocytopenia after the third dose of therapy, to share their approach for this case (Dogan 2011).

Braunlin evaluated cardiac function (Braunlin 2013). Clinical data were pooled from the phase I, phase I/II and phase III trials and analysed considering participants for whom data were available at all three study points (baseline, weeks 48 and 96, not including the randomised period) of galsulfase treatment. In spite of long-term enzyme therapy, cardiac valve stenosis and hypertrophy did not change in all individuals.

Between 2001 and 2002 a cross-sectional survey study of 121 people with MPS VI was conducted to establish demographics, urinary GAG levels and clinical progression of the disease. In 2013, a re-survey study was conducted to obtain repeat 10-year cross-

sectional data on those individuals that took part in the survey study (n = 59). A total of 55 individuals received galsulfase and the mean (standard deviation) treatment duration was 6.8 (2.2) years between baseline to follow up. Long-term patients treated with galsulfase were associated with improvements in pulmonary function and endurance. The 6MWT was considered to determine endurance, mobility and also to provide an indication of cardiopulmonary health. Those treated with galsulfase who completed the test had an improvement of 65.7minutes at follow up compared to baseline (P<0.0001). The levels of uGAG decreased by 87.9% in the participants treated with galsulfase (n=55) versus 49.8% in the untreated group (n =3) at follow up compared to baseline. Rates of overall mortality reduced among those treated with galsulfase versus the untreated group (16.5% versus 50.0%; unadjusted hazard ratio, 0.24 (95% CI 0.10 to 0.59) (Giugliani 2014). In general, these findings are aligned with the results from Harmatz study and show consistent improvements on the main outcomes in the long-term results of those treated with galsulfase (Harmatz 2006).

A systematic review on the same topic was published in 2009 (El Dib 2009). The authors declared to select and judge the literature using the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The employed methodology was similar, except for the inclusion of phase I/II in the review. Nevertheless, the authors could not perform a meta-analysis of them because they did not consider the same doses during the follow-up period. The criteria for data analysis that we considered was also different.

AUTHORS' CONCLUSIONS

Implications for practice

Only one randomised controlled study (with an overall unclear risk of bias) was included in this review and it failed to describe important outcomes that correspond to patients' vital functions, such as cardiac and respiratory function, or z scores for height and weight. Quality of life and mortality were not evaluated. Futher studies are required to obtain evidence on long-term effectiveness and safety of ERTwith galsulfase.

Implications for research

Further high quality studies need to be developed to look at: (i) long-term effects of ERT; (ii) galsulfase use in younger people; (iii) dose optimisation; and (iv) effect on cardiac and respiratory function, growth, quality of life and mortality.

ACKNOWLEDGEMENTS

We would like to thank Tracey Remmington and Natalie Hall from the Cochrane Cystic Fibrosis & Genetic Disorders Group for their help with the queries we have had throughout the review process.

We would like to thank Bernardo Garcia Oliveira Soares for his previous input (an author on the published protocol).

REFERENCES

References to studies included in this review

Harmatz 2006 *{published data only}*

Braunlin E, Rosenfeld H, Kampmann C, Johnson J, Beck M, Giugliani R, et al. Enzyme replacement therapy for mucopolysaccharidosis VI: long-term cardiac effects of galsulfase (Naglazyme®) therapy. *Journal of Inherited Metabolic Disease* 2013;**36**(2):385–94.

Guffon N, Harmatz P, Giugliani R, Schwartz I, Miranda C, Teles E, et al. A phase 3, randomized, double-blind, placebo-controlled, multicenter, multinational clinical study of recombinant human N-acetylgalactosamine 4 sulfatase (rhASB) in patients with mucopolysaccharidosis VI [abstract]. *Journal of Inherited Metabolic Disease* 2005;**28** (Suppl 1):190, Abstract no: 377-O. [CENTRAL: 1000734; CRS: 5500131000000076]

Harmatz P, Yu Z-F, Giugliani R, Schwartz IVD, Guffon N, Teles EL, et al. Enzyme replacement therapy for mucopolysaccharidosis VI: evaluation of long-term pulmonary function in patients treated with recombinant human N-acetylgalactosamine 4-sulfatase. *Journal of Inherited Metabolic Disease* 2010;**33**(1):51–60.

Harmatz P, Giugliani R, Schwartz I, Guffon N, Miranda CS, Teles E, et al. Long term benefit and safety with recombinant human arylsulfatase B (rhASB) ERT for MPS VI [abstract]. *Journal of Inherited Metabolic Disease* 2006;**29** (Suppl 1):29, Abstract no: WS-9-6. [CENTRAL: 1000733; CRS: 5500131000000075]

Harmatz P, Giugliani R, Schwartz IDV, Guffon N, Teles EL, Miranda MC, et al. Long-term follow-up of endurance and safety outcomes during enzyme replacement therapy for mucopolysaccharidosis VI: final results of three clinical studies of recombinant human N-acetylgalactosamine 4-sulfatase. *Molecular Genetics and Metabolism* 2008;**94**(4): 469–75.

* Harmatz P, Giugliani R, Schwartz, Guffon N, Teles EL, Miranda MC, et al. Enzyme replacement therapy for mucopolysaccharidosis VI: a phase 3, randomized, double-blind, placebo-controlled, multinational study of recombinant human N-acetylgalactosamine 4-sulfatase (recombinant human arylsulfatase B or rhASB) and follow-on, open-label extension study. *Journal of Pediatrics* 2006; **148**(4):533–9.

References to studies excluded from this review

Bagewadi 2008 *{published data only}*

Bagewadi S, Roberts J, Mercer J, Jones S, Stephenson J, Wraith JE. Home treatment with Elaprase and Naglazyme is safe in patients with mucopolysaccharidoses types II and VI, respectively. *Journal of Inherited Metabolic Disease* 2008; **31**(6):733–7.

Harmatz 2004 *{published data only}*

Braunlin E, Rosenfeld H, Kampmann C, Johnson J, Beck M, Giugliani R, et al. Enzyme replacement therapy for mucopolysaccharidosis VI: long-term cardiac effects of galsulfase (Naglazyme®) therapy. *Journal of Inherited Metabolic Disease* 2013;**36**(2):385–94.

Harmatz P, Giugliani R, Schwartz I, Azevedo AC, Guffon N, Miranda CS, et al. Update on clinical trial results in MPS VI [abstract]. *Journal of Inherited Metabolic Disease* 2004;**27**(Suppl 1):183, Abstract no: 360-O. [CENTRAL: 1000732; CRS: 5500131000000074]

Harmatz P, Giugliani R, Schwartz IDV, Guffon N, Teles EL, Miranda MC, et al. Long-term follow-up of endurance and safety outcomes during enzyme replacement therapy for mucopolysaccharidosis VI: Final results of three clinical studies of recombinant human N-acetylgalactosamine 4-sulfatase. *Molecular Genetics and Metabolism* 2008;**94**(4): 469–75.

Harmatz P, Kramer WG, Hopwood JJ, Simon J, Butensky E, Swiedler SJ. Mucopolysaccharidosis VI Study Group. Pharmacokinetic profile of recombinant human N-acetylgalactosamine 4-sulphatase enzyme replacement therapy in patients with mucopolysaccharidosis VI (Maroteaux-Lamy syndrome): a phase I/II study. *Acta Paediatrica Supplement* 2005;**94**(447):61–8.

* Harmatz P, Whitley CB, Waber L, Pais R, Steiner R, Plecko B, et al. Enzyme replacement therapy in mucopolysaccharidosis VI (Maroteaux-Lamy syndrome). *Journal of Pediatrics* 2004;**144**(5):574–80.

Harmatz P, Yu ZF, Giugliani R, Schwartz IVD, Guffon N, Teles EL, et al. Enzyme replacement therapy for mucopolysaccharidosis VI: evaluation of long-term pulmonary function in patients treated with recombinant human N-acetylgalactosamine 4-sulfatase. *Journal of Inherited Metabolic Disease* 2010;**33**(1):51–60.

Kakkis E. Enzyme replacement therapy for the mucopolysaccharidoses [abstract]. *Journal of Inherited Metabolic Disease* 2001;**14**(7):776. [CENTRAL: 461031; CRS: 5500050000000131]

Karageorgos L, Harmatz P, Simon J, Pollard A, Clements PR, Brooks DA, et al. Mutational analysis of mucopolysaccharidosis type VI patients undergoing a trial of enzyme replacement therapy. *Human Mutation* 2004;**23** (3):229–33.

Harmatz 2005 *{published data only}*

Braunlin E, Rosenfeld H, Kampmann C, Johnson J, Beck M, Giugliani R, et al. Enzyme replacement therapy for mucopolysaccharidosis VI: long-term cardiac effects of galsulfase (Naglazyme®) therapy. *Journal of Inherited Metabolic Disease* 2013;**36**(2):385–94.

Harmatz P, Giugliani R, Schwartz I, Azevedo AC, Guffon N, Miranda CS, et al. Update on clinical trial results in MPS VI [abstract]. *Journal of Inherited Metabolic Disease* 2004;**27**(Suppl 1):183, Abstract no: 360-O. [CENTRAL: 1000732; CRS: 5500131000000074]

Harmatz P, Giugliani R, Schwartz IDV, Guffon N, Teles EL, Miranda MC, et al. Long-term follow-up of endurance and safety outcomes during enzyme replacement therapy for mucopolysaccharidosis VI: Final results of three clinical studies of recombinant human N-acetylgalactosamine 4-sulfatase. *Molecular Genetics and Metabolism* 2008;**94**(4): 469–75.

* Harmatz P, Ketteridge D, Giugliani R, Guffon N, Teles EL, Miranda MC, et al. Direct comparison of measures of endurance, mobility, and joint function during enzyme-replacement therapy of mucopolysaccharidosis VI (Maroteaux-Lamy syndrome): results after 48 weeks in a phase 2 open-label clinical study of recombinant human N-acetylgalactosamine4-sulfatase. *Pediatrics* 2005;**115**(6): 681–9.

Harmatz P, Yu ZF, Giugliani R, Schwartz IVD, Guffon N, Teles EL, et al. Enzyme replacement therapy for mucopolysaccharidosis VI: evaluation of long-term pulmonary function in patients treated with recombinant human N-acetylgalactosamine 4-sulfatase. *Journal of Inherited Metabolic Disease* 2010;**33**(1):51–60.

Harmatz 2013 *{published data only}*

Harmatz PR, Garcia P, Guffon N, Randolph LM, Shediac R, Braunlin E, et al. Galsulfase (Naglazyme(R)) therapy in infants with mucopolysaccharidosis VI. *Journal of Inherited Metabolic Disease* 2014;**37**(2):277–87.

Pitz 2009 *{published data only}*

Pitz S, Ogun O, Arash L, Miebach E, Beck M. Does enzyme replacement therapy influence the ocular changes in type VI mucopolysaccharidosis?. *Albrecht von Graefes Archiv fur Klinische und Experimentelle Ophthalmologie [Graefe's Archive for Clinical and Experimental Ophthalmology]* 2009;**247**(7): 975–80. [CENTRAL: 700339; CRS: 5500050000000130; PUBMED: 19159944]

Additional references

Braunlin 2013

Braunlin E, Rosenfeld H, Kampmann C, Johnson J, Beck M, Giugliani R, et al. Enzyme replacement therapy for mucopolysaccharidosis VI: long-term cardiac effects of galsulfase (Naglazyme®) therapy. *Journal of Inherited Metabolic Disease* 2013;**36**(2):385–94.

Cardoso-Santos 2008

Cardoso-Santos A, Azevedo AC, Fagondes S, Burin MG, Giugliani R, Schwartz IV. Mucopolysaccharidosis type VI (Maroteaux-Lamysyndrome): assessment of joint mobility and grip and pinch strength. *Jornal of Pediatrica* 2008;**84** (2):130–5.

Decker 2010
Decker C, Yu ZF, Giugliani R, Schwartz IV, Guffon N, Teles EL, et al. Enzyme replacement therapy for mucopolysaccharidosis VI: Growth and pubertal development in patients treated with recombinant human N-acetylgalactosamine 4-sulfatase. *Journal of Pediatric Rehabilitation Medicine* 2010;**3**(2):89–100.

Deeks 2011
Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, editor(s) editor(s). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). Available from www.cochrane-handbook.org*. The Cochrane Collaboration, 2011.

Dogan 2011
Doğ an M, Cesur Y, Peker E, Oner AF, Dogan SZ. Thrombocytopenia associated with galsulfase treatment. *Human & Experimental Toxicology* 2011;**30**(7):768–71.

El Dib 2009
El Dib RP, Pastores GM. A systematic review of new advances in the management of mucopolysaccharidosisVI (Maroteaux-Lamy syndrome): focus on galsulfase. *Biologics* 2009;**3**:459-68.

Elbourne 2002
Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington HV, Vail A. Meta-analysis involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140–9.

Giugliani 2007
Giugliani R, Harmatz P, Wraith JE. Management guidelines for mucopolysaccharidosis VI. *Pediatrics* 2007;**120**(2): 2006–184.

Giugliani 2014
Giugliani R, Lampe C, Guffon N, Ketteridge D, Teles EL, Wraith JE, Jones SA, Piscia-Nichols C, Lin P, Quartel A, Harmatz P. Natural history and galsulfase treatment in mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy syndrome)-10-year follow-up of patients who previously participated in an MPS VI survey study. *Am J Med Genet Part A* 2014;**164**(8):1953-1964. [PUBMED: 24764221]

Higgins 2003
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. *BMJ* 2003;**327**: 555–557.

Higgins 2011
Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. Available from www.cochrane-handbook.org*. The Cochrane Collaboration, 2011.

Lowry 1990
Lowry RB, Applegarth DA, Toone JR, MacDonald E, Thunem NY. An update on the frequency of mucopolysaccharide syndromes in British Columbia. *Human Genetics* 1990;**85**(3):389–90.

Maroteaux 1963
Maroteaux P, Leveque B, Marie J, Lamy M. A new dysostosis with urinary elimination of chondroitin sulfate B. *Presse Medicale* 1963;**71**:1849–52.

Meikle 1999
Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. *JAMA* 1999;**281**(3):249–54.

Nelson 1997
Nelson J. Incidence of the mucopolysaccharidoses in Northern Ireland. *Human Genetics* 1997;**101**(3):355–8.

Neufeld 2001
Neufeld EF, Muenzer J. The Mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, Valle D editor(s). *The Metabolic and Molecular Bases of Inherited Disease*. 8th Edition. Vol. **3**, New York: McGraw-Hill, 2001:3421–52.

Pinto 2004
Pinto R, Caseiro C, Lemos M, Lopes L, Fontes A, Ribeiro H, et al. Prevalence of lysosomal storage diseases in Portugal. *European Journal of Human Genetics* 2004;**12**(2):87–92.

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Valayannopoulos 2010
Valayannopoulos V, Nicely H, Harmatz P, Tuberville S. Mucopolysaccharidosis VI. *Orphanet Journal of Rare Disease* 2010;**12**(5):5.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Harmatz 2006

Methods	Phase III, randomised, multicenter, placebo-controlled, double-blind study with 24-week extension period
Participants	39 participants with MPS VI. Inclusion criteria was age > 7 years with biochemical or genetic confirmation of MPS VI, ability to walk without assistance at least 5 meters and no more than 270 meters in the first six minutes, or no more than 400 meters in 12 minutes, in a 12MWT. Exclusion criteria were clinically significant spinal cord compression or a medical condition or other circumstance that could interfere with study compliance. Participants were randomised into 2 groups: 19 in rhASB group (7 males and 12 females, mean age 13.7 years); 20 participants in placebo group (6 males and 14 females, mean age 10.7 years). The length of the double-blind period was 24 weeks. An open-label 24-week extension study was conducted and all patients receiving placebo solution in the first 24-weeks were converted to receive rhASB solution
Interventions	1.0 mg/ml intravenous infusion of rhASB or placebo weekly.
Outcomes	*Primary outcomes*: 12MWT *Secondary outcomes*: 3MSC Change in GAGs urinary excretion *Other outcomes included*: Lung function Cardiac function Joint mobility Adverse effects
Notes	Funding sources: the study was sponsored by BioMarin Pharmaceutical Inc., and it was supported, in part, with funds provided by the National Center for Research Resources, 5 M01 RR-01271 (Dr Harmatz)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but the method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	Description of allocation concealment was not reported.

Incomplete outcome data (attrition bias) All outcomes	Low risk	The authors reported that safety analyses included all participants who received at least one dose of intervention and the efficacy analyses included all randomised participants (intention-to-treat analysis). They also declared that 11 randomised participants did not fulfil inclusion criteria (were not excluded)
Selective reporting (reporting bias)	Unclear risk	The outcomes were as described in the study protocol. The study did not show data from any of the other outcomes included, only declaring that rhASB had no effect in these endpoints
Other bias	Unclear risk	Despite randomization, the characteristics of the study participants were not similar between the two groups (participants in the placebo group were, on average, younger, shorter, and weighed less than those in the rhASB group, the authors declared that none of these differences was statistically significant). No other potential sources of bias were detected
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study stated that investigators and staff were not informed of the original treatment assignments
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study stated that investigators and staff did not participate in the efficacy assessments

3MSC: 3-minute stair climb
12MWT: 12-minute walk test
GAGs: glycosaminoglycans
rhASB: recombinant human *N*-acetylgalactosamine 4-sulfatase (recombinant human arylsulphatase B)

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bagewadi 2008	Case series.
Harmatz 2004	Phase I/II study.
Harmatz 2005	Phase II study.
Harmatz 2013	Phase IV study without control group
Pitz 2009	Case series.

DATA AND ANALYSES

Comparison 1. Galsulfase verus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 12MWT	1		Mean Difference (Fixed, 95% CI)	Totals not selected
1.1 at 24 weeks	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
2 3MSC	1		Mean Difference (Fixed, 95% CI)	Totals not selected
2.1 at 24 weeks	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
3 6MWT	1		Mean Difference (Fixed, 95% CI)	Totals not selected
3.1 at 24 weeks	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Respiratory tests	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 FVC	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 MVV	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 GAG Level	1		Mean Difference (Fixed, 95% CI)	Totals not selected
5.1 at 24 weeks	1		Mean Difference (Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Deaths	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Drug-related AEs	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Serious AEs	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.4 Severe AEs	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.5 AEs during infusion	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.6 Drug-related AEs during infusion	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Galsulfase verus placebo, Outcome 1 12MWT.

Review: Enzyme replacement therapy with galsulfase for mucopolysaccharidosis type VI

Comparison: 1 Galsulfase verus placebo

Outcome: 1 12MWT

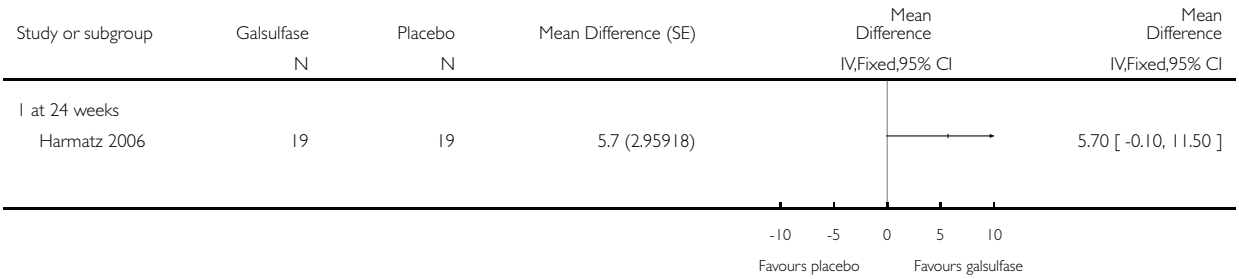
Study or subgroup	Galsulfase N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 at 24 weeks					
Harmatz 2006	19	19	92 (40.8163)		92.00 [12.00, 172.00]

Analysis 1.2. Comparison 1 Galsulfase verus placebo, Outcome 2 3MSC.

Review: Enzyme replacement therapy with galsulfase for mucopolysaccharidosis type VI

Comparison: 1 Galsulfase verus placebo

Outcome: 2 3MSC

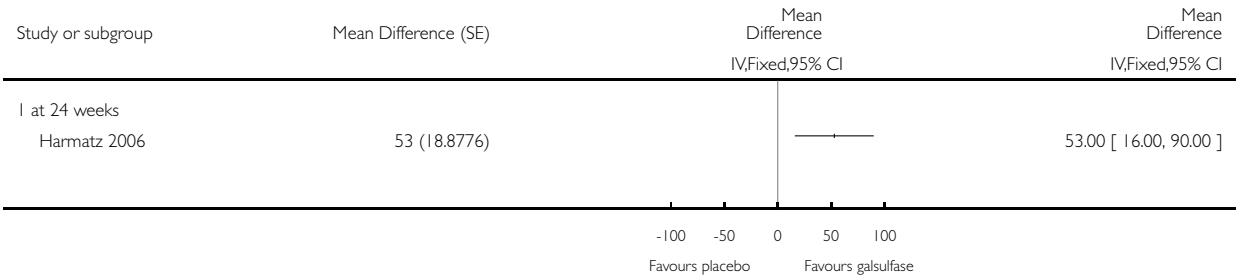


Analysis 1.3. Comparison 1 Galsulfase verus placebo, Outcome 3 6MWT.

Review: Enzyme replacement therapy with galsulfase for mucopolysaccharidosis type VI

Comparison: 1 Galsulfase verus placebo

Outcome: 3 6MWT



Analysis 1.4. Comparison 1 Galsulfase verus placebo, Outcome 4 Respiratory tests.

Review: Enzyme replacement therapy with galsulfase for mucopolysaccharidosis type VI

Comparison: 1 Galsulfase verus placebo

Outcome: 4 Respiratory tests

Study or subgroup	Galsulfase N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 FVC						
Harmatz 2006	19	-0.02 (0.13)	18	-0.01 (0.08)		-0.01 [-0.08, 0.06]
2 MVV						
Harmatz 2006	15	2.1 (6.3)	17	0.2 (4.9)		1.90 [-2.05, 5.85]

Analysis 1.5. Comparison 1 Galsulfase verus placebo, Outcome 5 GAG Level.

Review: Enzyme replacement therapy with galsulfase for mucopolysaccharidosis type VI

Comparison: 1 Galsulfase verus placebo

Outcome: 5 GAG Level

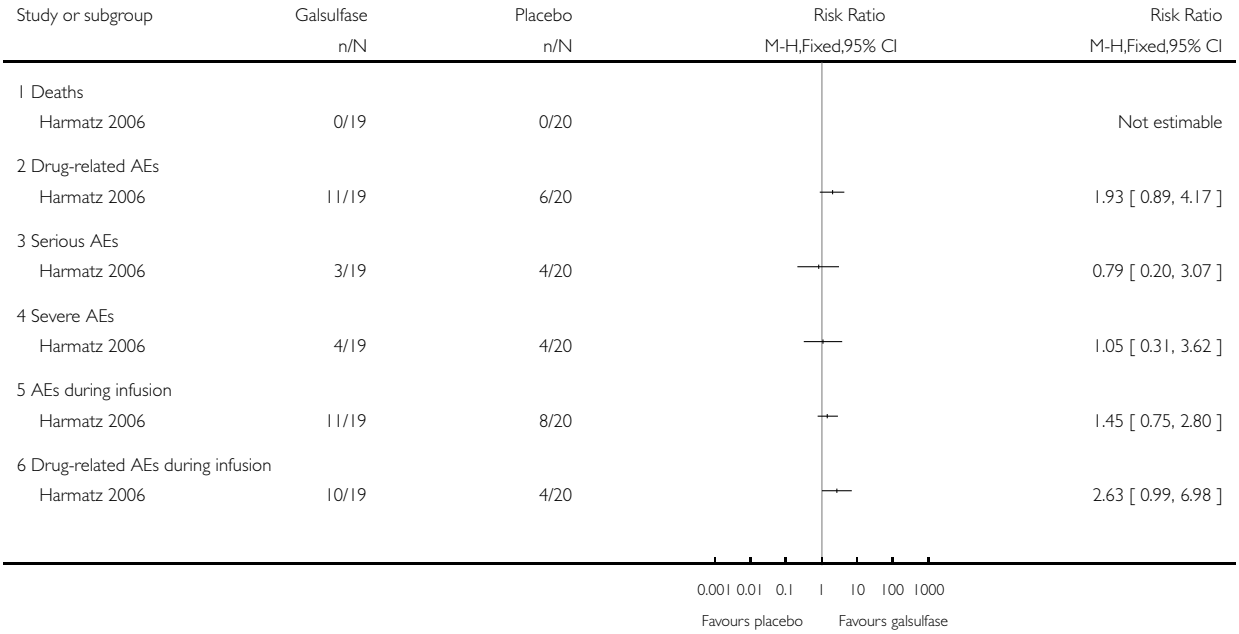
Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 at 24 weeks			
Harmatz 2006	-227 (18.8775)		-227.00 [-264.00, -190.00]

Analysis 1.6. Comparison 1 Galsulfase verus placebo, Outcome 6 Adverse events.

Review: Enzyme replacement therapy with galsulfase for mucopolysaccharidosis type VI

Comparison: 1 Galsulfase verus placebo

Outcome: 6 Adverse events



APPENDICES

Appendix 1. Glossary

Term	Explanation
Dysostosis multiplex	Specific pattern of radiographic changes observed in many lysosomal storage disorders
Hepatosplenomegaly	Enlargement of the liver and spleen. It can occur as a result of infection, storage disorders or malignancy

(*Continued*)

Skeletal dysplasia	Disorders in bone and cartilage development causing abnormalities of parts of or the entire skeleton
Autosomal recessive	One of several ways that a trait, disorder, or disease can be passed down through families
Dermatan sulphate	Also known as chondroitin sulphate B, is composed of linear polysaccharides assembled as disaccharide units containing N-acetyl galactosamine
Hematopoietic stem cell transplantation (HSCT)	Intravenous infusion of hematopoietic stem and progenitor cells to establish marrow and immune function
Pyrexia	Medical term for fever.
Exanthem	Widespread rash usually accompanied by fever, malaise and headache
Urticaria	Medical term for hives.

Appendix 2. CENTRAL search strategy

#1 Mucopolysaccharidosis VI
#2 Maroteaux-Lamy
#3 MPS VI
#4 "Mucopolysaccharidosis VI"[Mesh]
#5 #1 OR #2 OR #3 OR #4
#6 enzyme
#7 "Enzyme Replacement Therapy"[Mesh]
#8 #6 OR #7
#9 #5 AND #8
#10 randomised controlled trial [pt]
#11 controlled clinical trial [pt]
#12 randomised [tiab]
#13 placebo [tiab]
#14 drug therapy [sh]
#15 randomly [tiab]
#16 trial [tiab]
#17 groups [tiab]
#18 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19 animals [mh] NOT humans [mh]
#20 #18 NOT #19
#21 #9 AND #20

Appendix 3. MEDLINE search strategy

#1 Mucopolysaccharidosis VI
#2 Maroteaux-Lamy
#3 MPS VI
#4 "Mucopolysaccharidosis VI"[Mesh]
#5 #1 OR #2 OR #3 OR #4
#6 enzyme
#7 "Enzyme Replacement Therapy"[Mesh]
#8 #6 OR #7
#9 #5 AND #8
#10 randomised controlled trial [pt]
#11 controlled clinical trial [pt]
#12 randomised [tiab]
#13 placebo [tiab]
#14 drug therapy [sh]
#15 randomly [tiab]
#16 trial [tiab]
#17 groups [tiab]
#18 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19 animals [mh] NOT humans [mh]
#20 #18 NOT #19
#21 #9 AND #20

Appendix 4. LILACS search strategy

Mh:"Mucopolysaccharidosis VI" or "Mucopolisacaridosis VI" or "Mucopolissacaridose VI" or "Polydystrophic Dwarfism" or "Maroteaux-Lamy Syndrome" or Mh:C16.320.565.202.715.670$ or Mh:C16.320.565.595.600.670$ or Mh:C17.300.550.575.670$ or Mh:C18.452.648.202.715.670$ or Mh:C18.452.648.595.600.670$ or "Mucopolysaccharidosis VI" or "Maroteaux Lamy" or "MPS VI" or "Mucopolissacaridoses" and Mh: "Enzyme Replacement Therapy" or "Terapia de Reemplazo Enzimático" or "Terapia de Reposição de Enzimas" or Mh:E02.319.353.500$ or Mh:"Enzymes" or "Enzimas" or "Enzimas" or Mh:D08.811$

CONTRIBUTIONS OF AUTHORS

Marcela Junqueira Brunelli: the co-ordinator of this review and also responsible for its design and drafting the text (including a policy perspective, resulting from her knowledge of public health).

Álvaro Nagib Atallah: provided general advice on this review.

Edina MK da Silva: provided technical support during the production of the review.

DECLARATIONS OF INTEREST

Marcela Junqueira Brunelli: none known.

Álvaro Nagib Atallah: none known.

Edina MK da Silva: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- CAPES, Brazil.
- National Institute for Health Research, UK.

This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Due to cervical cord compression and myelopathy are recognised as features of the disease and were excluded from the outcome "adverse effects and toxicity of treatment".

INDEX TERMS

Medical Subject Headings (MeSH)

Enzyme Replacement Therapy [*methods]; Glycosaminoglycans [urine]; Mucopolysaccharidosis VI [*drug therapy; urine]; N-Acetylgalactosamine-4-Sulfatase [*therapeutic use]; Randomized Controlled Trials as Topic; Recombinant Proteins [therapeutic use]

MeSH check words

Humans